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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,531	08/30/2001	Carl Risinger	SGL-2020-UT	9953

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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,531	RISINGER ET AL.	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *82003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Response to Arguments

Applicant's election of Group II(claims 7-11) for examination without traverse in their remarks received 1/10/2005 is acknowledged as is their communication received 2/21/2005. Claims 1-6 have been cancelled, and therefore claims 7-11 are pending. While applicants filed no arguments in response to the restriction requirement, it should be clarified that the office's sending of a second restriction requirement was necessitated by applicant's amendment to claims 7-11 of their claims to recite the limitation of "3 or more SNPs". It wasn't until the interview on 11/13/2004, that both the examiner and Bruce Grant agreed that the typographical error necessitated the second restriction requirement(see 11/15/2004 interview summary).

Priority

Acknowledgement of claim to foreign priority of United Kingdom Application, 0021286.0, filed 08/30/2000 under 35 U.S.C. 119(a)-(d) has been made, however applicant should note that the certified copy of this foreign priority document has not yet been received and as a result the claim to foreign priority under the same has not yet been granted.

Claim interpretations

It should be noted that in the following art rejection the term "CYP2C19 flanking region" in the absence of any explicit definition in the specification, has been interpreted as meaning, any region next to another region either within the gene or on the 5' or 3' ends.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldstein et al.(Pharmacogenetics, 1997, 7; 59-64).

With regard to claim 7, the reference teaches a method for determining a human's capacity to metabolize a substrate of a CYP2C19 enzyme, which comprises:

Identifying nucleotides at two or more polymorphic sites in a CYP2C19 flanking region in a strand of a human nucleic acid and predicting the capacity from the nucleotides identified at the two or more polymorphic sites. The method specifically teaches the two mutations *CYP2C19m1*(splice mutation in exon 5) and *CYP2C19m2* (premature stop codon in exon 4) both in the "CYP2C19 flanking region" of exon 3, which account for 100% of the Oriental and 85% of Caucasian poor metabolizer(PM) alleles of mephenytoin, a substrate of the CYP2C19 enzyme.

With regard to claims 8-10, the method comprises isolating DNA nucleic acid that is single stranded from humans in their teaching of genotyping procedures on page 60 bridging page 61 wherein genomic DNA was purified from 200ul of whole blood and detection of the normal and defective alleles was performed by PCR-restriction enzyme analysis. Both alleles were then determined in extensive metabolizers(EMs) and PMs to determine allele frequencies.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining a Caucasian human's capacity to metabolize omeprazole, a substrate of the CYP2C19 enzyme, by identifying the two polymorphic sites at positions 352 and 1060 of SEQ ID NO:1, but does **not** reasonably provide enablement for;

- Detecting any race of human's capacity to metabolize a substrate of CYP2C19 through the identification of two or more polymorphic sites in the CYP2C19 gene.
- Detecting the above capacity to metabolize any substrate of CYP2C19, besides omeprazole.
- Detecting any two or more polymorphic sites in any CYP2C19 flanking region.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

> They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 7-10 are broadly drawn to a method of determining a human of any race's capacity to metabolize any substrate of CYP2C19 through the identification of any two or more polymorphic sites in any flanking region of CYP2C19. The claims are so broad as to encompass the method's execution with; any SNP located in a "CYP2C19 flanking region", any race of human having these broadly recited SNPs, and detecting the above capacity to metabolize any substrate of CYP2C19. However, as will be further discussed, there is no support in the specification and prior art for the methods as broadly as they are currently claimed. The invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites that "for these experiments, a single dose of 20 mg omeprazole(Losec, AstraZeneca) was given in the morning after an overnight fast"(lines 10-12 pg. 13), and furthermore that "in the first part of the study, approximately 90 samples(Swedish Caucasians) were selected as set forth in Table 1"(Spec pg. 13). In table 11, the specification teaches the statistically relevant p-values of haplotypes H1-H3 as defined in Table 10 also on page 19 of the specification. In table 13 on page 20, the specification teaches the CYP2C19 genotypes and haplotypes that are associated with a particular capacity to metabolize

omeprazole, the only taught substrate of CYP2C19(i.e. Ultra Extensive Metabolizers(UEM), Extensive metabolizers(EM), Intermediate metabolizers(IM), or Poor metabolizers(PM) along with the observed metabolic ratios of omeprazole. However, there is no teaching of any other SNP in the flanking region of CYP2C19, besides those enumerated in Table 10, that are associated with an observed capacity to metabolize omeprazole. Furthermore, only a single population of Swedish Caucasians is taught to be a part of the specification's findings. Lastly, only omeprazole is taught as a substrate of CYP2C19 to yield these metabolic capacities. The specification omits any teachings of results obtained with a diverse population of all races, testing for metabolic capacities achieved by treatment with a diverse group of substrates of CYP2C19 other than omeprazole, and any SNP located in the flanking region of CYP2C19.

First, regarding the unpredictability associated with claiming any SNP located in the flanking region of CYP2C19, there exists a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be

disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated. As a result, there is a great deal of unpredictability that exists in the invention without any guidance in the specification for example, to any polymorphism located in the flanking region of CYP2C19 gene other than those enumerated in Table 10 of the specification, being correlated to any metabolic capacity. With respect to the unpredictability involved with the claims recitations of this method being applicable to a human of any race, additional prior art corroborates the unpredictability in Goldstein et al's teaching that "the frequency of this polymorphism[that of CYP2C19] varies markedly in different racial populations, with the PM phenotype representing 2-5% in Caucasian populations, but from 13-23% in Oriental populations"(Pharmacogenetics, 1997, 7; page 59 bottom right). Goldstein et al. further teach that "the present results indicate complete concordance between phenotype and genotype in three Oriental racial groups, while the incidence of the CYP2C19m1 allele is higher in Oriental races than in Caucasians or African-Americans...Saudi Arabians were found to resemble Caucasians in both the incidence of CYP2C19m1 and relative absence of CYP2C19m2"(Goldstein et al, Pg 63 bottom left side). Concerning the substrate being claimed, applicant provides no teaching of a general quality had by every substrate that their claim presently reads on. As a result, the presently filed specification provides enablement for only that of omeprazole.

The post filing date art further supports the unpredictability involved in extrapolating the results of a study with one distinct Caucasian population to all races as Ozawa et al. teach "that it

is a matter of primer importance to take interracial differences into account in the frequency of genetic polymorphisms of drug-responsive genes"(Introduction, Drug Metab. Pharmacokin. 19(2); 83-95(2004). The reference continues by teaching that ethnic differences in "Chinese, African, Swedish, and Spanish are schematically outlined in Fig. 1...that clearly indicated the existence of a considerable number of poor metabolizers showing high metabolic ratios in European Causasians(Swedish and Spanish) at a frequency of approximately 7% but PMs are relatively rare in the Chinese(1%)"(Page 84 left side).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there are a significant number of parameters which would have to be studied to apply this method to the broadly claimed embodiments involving any SNP in the flanking region of CYP2C19, in any race, and with any substrate to CYP2C19. The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention as asserted by the specification, one would have to establish a relationship between non-existent SNPs in the undefined region flanking CYP2C19 with some capacity to metabolize omeprazole, or some other substrate of CYP2C19. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients of all races as well as possible hundreds of pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would still be detected considering the new diversity of experimental variables, and further in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method is useful as broadly as it is claimed, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the

polymorphism in any race and to any capacity for metabolism. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of the method using any SNP in the region flanking the CYP2C19 gene, using any population other than a Swedish Caucasian one, to detect a capacity for metabolizing any substrate other than opremazole.

Guidance in the Specification.

The specification provides no evidence that the disclosed method would be effective if practiced as broadly as it is claimed. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that "for these experiments, a single dose of 20 mg omeprazole(Losec, AstraZeneca) was given in the morning after an overnight fast"(lines 10-12 pg. 13), and furthermore that "in the first part of the study, approximately 90 samples(Swedish Caucasians) were selected as set forth in Table 1"(Spec pg. 13). In table 11, the specification teaches the statistically relevant p-values of haplotypes H1-H3 as defined in Table 10 also on page 19 of the specification. In table 13 on page 20, the specification teaches the CYP2C19 genotypes and haplotypes that are associated with a particular capacity to metabolize omeprazole, the only taught substrate of CYP2C19(i.e. Ultra Extensive Metabolizers(UEM), Extensive metabolizers(EM), Intermediate metabolizers(IM), or Poor metabolizers(PM) along with the observed metabolic ratios of omeprazole. Even if, arguendo, the detected SNPs in the flanking region of CYP2C19 are correlated with some capacity of metabolism, there is no support for the same, prophetic correlation in any race being studied.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the use of SNPs to detect disease states is even further unpredictable, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Allowable Subject Matter

Claim 11 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris

3/3/2005

JEFFREY FREDMAN
PRIMARY EXAMINER
3/4/05